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Reducing the stigma of long acting injectable antipsychotics – current concepts and future developments*

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ABSTRACT

Background: Long acting injectable antipsychotics (LAI-APs) are considered a major advance in psychiatric treatment concerning treatment adherence and outcomes. Yet, both, doctors and patients remain sceptical.

Aim: To explain the rationale for using LAI-APs, review their effectiveness and explore barriers to use.

Method: Clinical overview of LAI-APs from the patient and doctor's perspective.

Results: LAI-APs were developed to increase adherence to treatment, thereby improving treatment outcomes. LAI-APs may reduce the risk of relapse and hospitalisation. Yet, the evidence from the few meta-analyses available remains weak. Both patients and doctors may associate LAI-APs with stigma and coercion. Current means of improving adherence include more focus on the therapeutic relationship, better information, adverse effects minimisation and half-life extension of LAI-APs. Future means of improving adherence include novel administration techniques that abolish the need for injection.

Conclusions: For both, clinicians and drug developers, drug adherence remains a major target for improving treatment outcomes.

KEYWORDS

Antipsychotics; long-acting injections; adherence; relapse; blood-brain-barrier

The rationale for long acting injectable (LAI) antipsychotics

The introduction of antipsychotics (AP) in the early 1950s heralded a start of a new era for the treatment of schizophrenia. For the first time, drugs became available that could effectively treat the positive symptoms of schizophrenia, including delusions, hallucinations and thought disorder. These first-generation antipsychotics (FGAs) significantly reduced or even eliminated harsh and ill-fated treatment attempts such as convulsive therapies or physical restraints [1]. Yet, despite the initial therapeutic success, it soon emerged that many patients only poorly adhered to these novel oral formulations [2]. This prompted the development of LAI-APs in the early 1960, first as fluphenazine and haloperidol deaconate. With the advent of second generation antipsychotics [2], LAI-FGAs use declined. But despite improved tolerability, adherence to oral SGAs did not prove any better than to oral FGAs. LAI-SGAs were developed once again to improve adherence rates [2]. Thus, the goal of LAI treatment has remained the same, to improve adherence as a means to reduce the risk of symptom exacerbation, relapse and hospitalisation [3,4].

Non-adherence to oral APs

Non-adherence to oral APs (OPAs) remains high. Estimates vary between 40–90% [3]. Non-adherence may explain treatment resistance in a significant number of patients. In a study of 99 patients, thought to be treatment resistant on OAPs, 35% had sub-therapeutic or undetectable plasma levels. Patients with sub-therapeutic or undetectable plasma levels were about three times more likely to be admitted to hospital [4].

Adherence to OAPs can be notoriously difficult to establish. Both patients and clinicians may over-report or overestimate adherence. A study conducted in 52 outpatients with schizophrenia or schizoaffective disorder compared four measures of adherence. These included patient self-reports, clinician estimates, pill count and a medication event monitoring system (MEMS). Via a microprocessor in the cap, MEMS recorded when and how often a medication bottle was opened. Adherence estimated varied with measure; 95% for patient self-reports, 76% for clinician estimates, 74% for pill count, and 48% for MEMS [5].

Effectiveness of SGR LAIs

Several studies have shown that LAI-APs may reduce the risk of relapse and hospitalisation. There is also some preliminary evidence that LAIs may reduce comorbid violent behaviour in patients with schizophrenia [6,7].

LAI risperidone

A randomised controlled trial (RCT) compared oral and LAI risperidone in 83 patients with recent onset of schizophrenia. The risk of exacerbation and/or relapse was significantly lower in patients treated with LAI-risperidone (7%) than with oral risperidone (50%) within one year. Mean time to relapse was significantly longer [8]. Another retrospective study showed that LAI-risperidone significantly reduced the admissions and length of stay [9].

LAI-paliperidone

In a prospective study of 210 patients being consecutively prescribed paliperidone palmeate, 65% of the patients were still receiving the LAI formulation after one year [10]. In a further prospective follow-up of 225 patients treated with paliperidone palmitate, 42% were still retained on the medication after two years. In this study, there was also a significant reduction of mean bed days. They decreased from 79.6 in the two years before to 46.2 in the two years after start of paliperidone palmitate [11]. Bressington et al. 2015 also found a significant reduction of bed days after paliperidone palmitate initiation [12]. In a multicentre randomised controlled trial of paliperidone palmitate against oral APs, risk of relapse within 24 months was reduced by 29% with the LAI. Time to relapse was also significantly longer in the LAI than in the oral AP group [13].

LAI aripiprazole

In a prospective study of 160 patients consecutively treated with aripiprazole LAI, 51% still received the agent after one year. Mean number of admissions fell significantly from 0.71/patient/year in the three years before to 0.45/patient in the year after aripiprazole LAI initiation. Equally significantly decreased mean number of bed days from 30.4/patient in the three years before to 22.8/patient in the year after aripiprazole LAI initiation. Median bed days fell from 21.7 to zero in the same time frame [14].

Meta-analyses

There are few meta-analyses. These show conflicting results and are less optimistic. The most recent meta-analyses stem from 2016 and 2017 [15,16]. Kishi et al. compared LAI- SGAs with OAPs in patients with recent-onset psychotic disorder. This analysis, including five RCTs conducted between 2009 and 2015, concluded that LAI-APs were not superior preventing the relapse but outperformed OAPs in terms of adherence and discontinuation due to ineffectiveness. LAI-APs had

a higher incidence of at least one adverse effect and tremor [15]. Ostuzzi et al. compared LAI-FGAs and SGAs with OAPs from 18 RCTs conducted between 1964 and 2015. This study concluded that there was no robust evidence for better tolerability and efficacy of LAI-APs [16]. However, patients with better adherence may be more likely to participate in trials. Selection bias may then reduce any potential difference between OAPs and LAI-APs.

Obstacles to LAIs use

Both patients and clinicians may reject LAI-APs. Reasons partly overlap. In a survey of 317 psychiatrists, 69% regarded LAI-APs less acceptable to the patients, 48% as stigmatising, 40% as old fashioned and 38% more prone to adverse effects [17]. Patients may indeed associate LAIs with stigma and coercion [18]. Fear of needles and injection pain may also shape negative attitudes towards LAI-APs [19].

In a study of 222 outpatients with schizophrenia or schizoaffective disorder, 43% currently treated with LAI-APs preferred this route of administration [20]. Conversely, only 6% currently treated with tablets would have preferred LAI-APs. Prior negative experience with AP and particularly LAI-AP treatment affected attitudes towards LAI-APs. Type of formulation may not drive attitudes towards AP. Need for treatment and symptom attribution to the underlying mental illness predicted apposite attitude towards antipsychotics. Extrapyramidal side effects shaped a negative attitude [20].

Overcoming barriers to LAI use

Information about LAI-APs and a good therapeutic relationship may promote LAI-APs use. In this context, it may be particularly important to rectify possible misconceptions about LAI-AP use. Patients may not know that LAI options exist, or they may associate injections with higher costs and even with addiction [18]. Doctors, on the other hand, may believe that LAI-APs cannot be used in first episode psychosis [21].

Minimising adverse effects

Choosing SGA LAI-APs over FGA LAI-APs and refraining from excessive doses may improve adherence. The use of FGA LAI-APs is particularly associated with tardive dyskinesia. Up to 11% of the patients may be affected [22]. Using FGAs LAI-APs in escalating doses is therapeutically counter-productive. Optimising haloperidol deaconate dosing illustrates this. At a dose of haloperidol deaconate 100mg/4weeks, corresponding to a daily total dose of 5 mg of oral haloperidol, about 90% of all the patients remain well. At a dose of haloperidol deaconate 300mg/4weeks, corresponding to a daily total dose of 30 mg of oral haloperidol, about 92% of all patients remain well. There is only marginal improvement in relapse prevention. But there is a much higher risk dose-dependent of extrapyramidal side effects [23]. Changing the formulation of LAI-APs is a way of preventing adverse effects associated with the injection itself. Oil-based formulations used in LAI-FGAs are more likely to cause scar tissue, when

Table 1. Summary of form of active drugs and formulation details of different LAIs available in the US, UK and EU (modified from Remenar 2014) [29].

Active drug in LAI-APs	Form of drug in the product	Formulation of LAI-APs
LAI-FGAs		
Fluphenazine	Decanoate prodrug	Solution in sesame oil
Haloperidol	Decanoate prodrug	Solution in sesame oil
Pipothiazine	Palmitate prodrug	Solution in sesame oil
Zuclopenthixol	Decanoate prodrug	Solution in sesame oil
Perphenazine	Decanoate prodrug	Solution in sesame oil
LAI-SGAs		
Risperidone	Free base	Polymeric microspheres (aqueous formulation)
Olanzapine	Pamoate salt	Freeze dried powder for aqueous suspension
Paliperidone	Palmitate prodrug	Nanocrystals in aqueous suspension
Aripiprazole	Monohydrate	Powder for aqueous suspension
Aripiprazole	Lauroxil ester prodrug	Ready-to-use aqueous suspension

LAI-APs: long-acting injectable antipsychotics; LAI-FGAs: long-acting injectable first-generation antipsychotics; LAI-SGAs: long-acting injectable second-generation antipsychotics.

used long-term. All later LAI-SGAs may minimise injection-related adverse effects by using aqueous solutions instead (Table 1).

Extending half-life

Extending the half-life of LAI-APs may be another effective way to improve adherence. Besides this, a longer half-life may extend the time to relapse once a LAIs is discontinued [24]. Experience from the Maudsley Hospital in London shows that only few patients discontinue LAI paliperidone given at a three-monthly interval. Advantages must be offset against the disadvantage. On one hand, longer half-life LAI-APs mean fewer injections overall, more autonomy, fewer visits to mental health facilities and lower risk of admission. On the other hand, longer half-life LAIs may be perceived as high dose with an increased risk of adverse events. Further potential draw-backs include loss of regular contact with the community mental health team. Injection pain due to administration of a higher volume may be a further disadvantage.

New ways of delivering LAI-APs

The concept of using LAI-APs to improve adherence and reduce the risk of relapse remains appealing but meta-analytic evidence is inconclusive. Patients and doctors remain sceptical as well. LAI-FGAs were all oil-based. Developing formulations that are long-acting but not injectable (LANI-APs) may be another way to improve outcomes. Such novel formulations could do away with the unpleasantness of injection. If delivery to the brain could be optimised, they might also reduce the amount of drug to be administered. Finally, some formulations could make administration reversible, a significant advantage if faced with serious adverse event such as neuroleptic malignant syndrome. Here, we present and discuss some of the novel techniques of drug delivery that may become available in the future.

Drug administration via nasal cavity

Drug administration via nasal cavity provides rapid absorption into systemic circulation and avoidance of enzymatic degradation and first pass effect. Compared to oral delivery, intranasal delivery results in rapid onset of activity and enhanced bioavailability. Drugs can be targeted to the brain directly through olfactory and trigeminal nerve ending regions bypassing the blood-brain-barrier (direct pathway). This is a way to increase drug delivery to the brain and hence efficacy. At the same time, drug delivery to the periphery is decreased. This can potentially alleviate the risk of systemic adverse effects such as cardiovascular or metabolic problems [25]. Reduced systemic concentrations may also benefit patients with severe renal or hepatic impairment. There is no antipsychotic substance approved or under examination in clinical trials based on intranasal drug delivery for brain targeting. However, there has been a great interest among the researchers in exploiting the benefits of intranasal brain targeting. This has resulted in the development of novel drug delivery approaches like solid lipid nanoparticles, polymeric nanoparticles or nanoemulsions [26]. For example, intranasal administration olanzapine loaded- PLGA microparticles to rats showed higher brain concentration (>10 times) of the drug as compared to the IV solution [27]. Specialised devices such as OptiNose and ViaNase electronic atomizer have also been developed to administer different drugs to middle and upper posterior regions of the nose for enhanced brain targeting. These studies showed a great potential for intranasal drug delivery of antipsychotics. But translating this research into successful clinical products depends on the local and systemic toxicity and safety of the drug loaded nanoparticulate systems. Long-term effects of higher concentrations of the drug in brain should also be studied.

Drug loaded implants

While LAI-APs may enhance the compliance and decrease the morbidity and mortality as compared to OAPs, depot injections are irreversible and thus lack flexibility clinical management. Besides, some LAI-APs can cause prolonged pain and scar tissue at the injection site. This coupled with a perceived stigma of injections can result in treatment discontinuation. Drug loaded implants for subcutaneous administration offer an alternative and novel drug delivery option for very long-term delivery of APs. Contrary to injectable drugs, implants could be removed after disposition. This reversibility of administration could be a significant advantage when managing risks of severe adverse drug reactions such as neuroleptic malignant syndrome. No product based on this technology is yet on the market, but clinical trials are under way. In a recent study on pharmacokinetics and safety of risperidone subcutaneous implants in patients with schizophrenia, therapeutic drug levels were quickly achieved and maintained near constant rates over six months [28]. This demonstrating the viability and potential of this new technology.

Conclusions

LAI-APs are an important clinical tool for improving adherence. Yet many patients and doctors perceive LAI-APs as coercive, old-fashioned and stigmatising. Means of overcoming barriers to LAI-AP use include a good therapeutic relationship, use of SGA-LAIs over FGA-LAIs and avoidance of excessive doses to minimise adverse effects. Novel intra-nasal and implant formulations may remove disadvantages of injectable such as irreversibility over several weeks, injection pain and scar tissue formation. Such novel formulations could also help to change the reputation of APs from old fashioned to high tech.

Disclosure statement

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Sitaram Velaga declares that there is no conflict of interest.

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